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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/625,085	07/23/2003	Sabine Gratzer	DEAV2002/0051US NP	5941

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EXAMINER	
JOIKE, MICHELE K	

ART UNIT	PAPER NUMBER
1636	

NOTIFICATION DATE	DELIVERY MODE
09/21/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/625,085	GRATZER ET AL.	
	Examiner	Art Unit	
	Michele K. Joike, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-13 and 16-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-13 and 16-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 28, 2007 has been entered.

Claims 1, 12, 13 and 18 are amended. Claims 2, 14, and 15 are canceled. Claims 1, 3-13 and 16-20 are pending and under consideration in the instant application. Any rejection of record in the previous Office Action, mailed November 3, 2006, that is not addressed in this action has been withdrawn.

Response to Arguments Concerning Claim Rejections – *35 USC § 103 (a)*

Applicants' arguments filed on May 3, 2007 have been fully considered. The following grounds of traversal are presented:

1. US 6,063,578 teaches a plasmid system comprising dual reporters for the independent evaluation of transcription and replication, wherein the effect of the transcriptional regulator on the second reporter gene should be less than 50% of the effect on the first reporter gene. Applicants teach a double reporter assay to improve signal-to-background ratio.

2. US 20050118690 teaches a dual reporter assay, but does not teach a method of improving signal-to-background ratio.

3. There is no motivation to combine US 6,063,578 with any of the references because US 6,063,578 id directed to a dual reporter assay permitting independent evaluation of transcription and replication.

Applicants' traversal has been fully considered and found to be persuasive in that US 6,063,578 does not teach a double reporter assay to improve signal-to-background ratio. However, applicants' amendment has necessitated the new grounds of rejection under 35 U.S.C. 102(b) and 35 U.S.C. 103(a) recited below, except for claim 18, which does not include the limitation of improving signal-to-background ratio.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3-5, 10-13, 16, 17 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Brown et al.

Applicant claims a method of identifying an agent that modulates the activity of a target molecule utilizing a dual reporter assay for improving signal to background ratio by contacting a cell and modulating a target molecule. The cell comprises a growth marker and a reporter coding for an enzyme. After contact by agent, cell propagation

and reporter activity are measured. The target molecule affects the reporter gene, and is further limited to a heterologous molecule and can be a nucleic acid or polypeptide. The target molecule affects cellular propagation indirectly or through an intermediary molecule. The target molecule can also affect the reporter gene and cellular propagation directly. The reporter gene produces an enzyme. The cell is a yeast cell, specifically *S. cerevisiae*.

Brown et al (Yeast 16: 11-22, 2000, specifically, pp. 12-14, 16, 19 and Table 3) teach a dual reporter assay for evaluating chimeric yeast/mammalian Gα proteins in *S. cerevisiae*. Gα proteins can modulate effectors to cause signal propagation. GPCRs can also directly affect propagation. Table 3 lists the different concentrations of agonists used to determine the effect on the pheromone response pathway. The two reporter constructs used are FUS1-HIS3 and FUS1-lacZ. As stated in the specification on page 10, when these two constructs are combined, the improved signal-to-background ratio is 100-150:1. Therefore, FUS1-HIS3 and FUS1-lacZ have the inherent property of improving signal-to-background ratio. A beta-galactosidase assay is performed with CPRG as the substrate to measure activity. CPRG is converted to chlorophenol red after 24 hrs. of incubation. Cell growth is also determined. The cells were also disrupted to perform a Western blot. Glass beads are used to disrupt the membrane.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 18 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Crossin et al in view of US 6,063,578 and in further view of US 20050118690.

Applicant claims a method of identifying an agent that modulates the activity of a target molecule, wherein the agent contacts a cell and modulates the target molecule, and wherein said cell also comprises two reporter genes. After contact by agent, cell propagation and reporter activity are measured. The reporter genes produce a growth marker reporter and a reporter that is an enzyme. Measuring reporter activity comprises disrupting the cell by permeabilizing the membrane, or destroying the membrane. They also claim a second cell with a target molecule and reporter gene. After contact by agent, cell propagation and reporter activity are measured.

Crossin et al (PNAS 94: 2687-2692, 1997, specifically Abstract, Introduction, last paragraph, Exptl. Procedures, 2nd, 7th and last paragraph and Figure 4) teach a method of identifying an agent that modulates the activity of a target molecule by contacting a cell and modulating a target molecule, wherein an agonist, N-CAM, modulates a target molecule, GRE, which induces a luciferase reporter. N-CAM inhibits cell proliferation. In measuring luciferase activity, cells were lysed. They also teach a second cell with a

second target molecule, CM-V and a second reporter beta-galactosidase. N-CAM is the agonist. However, Crossin et al do not teach the use of two reporters.

US 6,063,578 (specifically columns 8-10) teach a dual reporter assay. Two different reporters need to be used. Enzymatic and fluorescent proteins are taught. It also is stated that the precise reporter genes used are not critical as long as expression can be detected.

US 20050118690 (specifically paragraphs 92 and 93) teach a dual reporter assay for isolating transformants. US 20050118690 teach that it is preferable to have two reporter genes within the cell. One reporter gene, when expressed, provides a growth advantage to transformed cells that are expressing the variant regulator protein, like LEU2, HIS3, LYS2, TRP1, URA3 or ADE2. This allows for the isolation of such transformants though selective pressures. The other reporter gene provides a colorimetric marker, such as the lacZ gene and its encoded protein, beta.-galactosidase. Alternatively, the second reporter provides a fluorescent or luminescent marker, such as green fluorescent protein (GFP).

The ordinary skilled artisan, desiring to use a dual reporter system, would have been motivated to combine the teachings of Crossin et al teaching a method of identifying an agent that modulates the activity of a target molecule, which induces a reporter, with the teachings of US 20050118690 teaching a dual reporter system with LEU2, HIS3, LYS2, TRP1, URA3 or ADE2 as the first reporter and lacZ or GFP as the second reporter, and with the teachings of US 6,063,578, teaching a dual reporter system because US 6,063,578, states that the dual reporter system allows for

observation of more than one change induced by a candidate agent. For example, one reporter can indicate whether there is a change in replication, while the second reporter can indicate whether there is a change in transcription. It would have been obvious to one of ordinary skill in the art to use dual reporters because both processes occur on the same molecule, which more accurately reflects the natural environment. Given the teachings of the prior art and the level of the ordinary skilled artisan at the time of the applicant's invention, it must be considered, absent evidence to the contrary, that said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Claims 1, 3-11, 13-14 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Keating et al in view of US 20050118690 and in further view of Yang et al.

Applicant claims a method of identifying an agent that modulates the activity of a target molecule wherein the agent contacts a cell and modulates the target molecule, and wherein said cell also comprises two reporter genes. After contact by agent, cell propagation and reporter activity are measured. One of the reporter genes produces an enzyme, and the substrate of the enzyme is added after a delay, specifically at least two cell cycles. Measuring reporter activity comprises disrupting the cell by permeabilizing the membrane, or destroying the membrane.

Keating et al (Oncogene 20: 4281-4290, 2001, specifically Introduction, p. 4282 and Materials & Methods, 1st and 6th paragraphs) teach a method of identifying an agent that modulates the activity of a target molecule by contacting a cell and modulating a

target molecule, wherein an agent, EGF, modulates a target molecule, ATM (a heterologous kinase), which induces a luciferase reporter. ATM is known to be involved in cell cycle control (see Abstract & Introduction). Cells were incubated with EGF for 16 hours before cells extracts were prepared. EGF was added during log phase, therefore at least one or two cell cycles have occurred. Firefly luciferase substrate (LARII) was added and reporter activity was measured using a Dual Luciferase Assay. However, Keating et al do not teach the use of two different reporters or improving signal-to-background ratio.

US 20050118690 (specifically paragraphs 92 and 93) teach a dual reporter assay for isolating transformants. US 20050118690 teach that it is preferable to have two reporter genes within the cell. One reporter gene, when expressed, provides a growth advantage to transformed cells that are expressing the variant regulator protein, like LEU2, HIS3, LYS2, TRP1, URA3 or ADE2. This allows for the isolation of such transformants though selective pressures. The other reporter gene provides a colorimetric marker, such as the lacZ gene and its encoded protein, beta.-galactosidase. Alternatively, the second reporter provides a fluorescent or luminescent marker, such as green fluorescent protein (GFP). However, it does not teach using two reporters to improve signal-to-background ratio.

Yang et al (J. Biol. Chem. 273(14): 8212-8216, 1998, specifically p. 8212, 8214, 8216) teach a dual fluorescent assay for improving signal-to-background ratio. Specifically, they teach optimizing GFP and BFP to enhance expression levels.

The ordinary skilled artisan, desiring to use a dual reporter system to improve signal-to-background ratio, would have been motivated to combine the teachings of Keating et al teaching a method of identifying an agent that modulates the activity of a target molecule, which induces a reporter and delays adding the substrate of a reporter, with the teachings of US 20050118690 teaching a dual reporter system with LEU2, HIS3, LYS2, TRP1, URA3 or ADE2 as the first reporter and lacZ or GFP as the second reporter, and with the teachings of Yang et al teaching a dual reporter system for improving signal-to-background ratio because Yang et al states that enhancing optimization of two reporters allows for maximum signal intensity. It would have been obvious to one of ordinary skill in the art to improve signal-to-background ratio because higher expression yields provide greater sensitivity. Given the teachings of the prior art and the level of the ordinary skilled artisan at the time of the applicant's invention, it must be considered, absent evidence to the contrary, that said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Allowable Subject Matter

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michele K. Joike, Ph.D. whose telephone number is 571-272-5915. The examiner can normally be reached on M-F, 9:00-6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Michele K Joike, Ph.D.
Examiner
Art Unit 1636

DAVID GUZO
PRIMARY EXAMINER